ORIGINAL ARTICLE

Gonorrhoea in London: usefulness of first line therapies

C A Ison, I M C Martin, for the London Gonococcal Working Group

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See end of article for authors' affiliations

Correspondence to: Dr C A Ison Medical Microbiology, Department of Infectious Diseases and Microbiology, Faculty of Medicine, Imperial College of Science, Technology and Medicine, St Mary's Campus, London W2 1PG, UK; c.ison@ic.ac.uk

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Objectives: To determine the true prevalence and patterns of resistance of *Neisseria gonorrhoeae* to antimicrobial agents used for therapy in London.
Methods: A longitudinal study of a representative sample of isolates of *N gonorrhoeae* linked to demographic data of infected patients was undertaken. Isolates were collected from consecutive patients attending genitourinary medicine clinics in the North and South Thames regions of London during 3 months of each of 4 years, 1997–2000. Prevalence of plasmid mediated resistance to penicillin and chromosomally mediated resistance to penicillin and ciprofloxacin was determined by susceptibility testing. The association of antimicrobial resistance among gonococci with sexual orientation of the patient and country of acquisition of infection was determined.
Results: Numbers of gonococcal isolates collected over the same time period between 1997–2000 have increased by 74%. Plasmid mediated resistance to penicillin was low but has risen above 5% in 2000. Chromosomal resistance to penicillin has fallen below the 5% level but total resistance to penicillin, plasmid and chromosomally mediated, was above 5% in all 4 years. The incidence of resistance and reduced susceptibility to the alternative therapeutic choice, ciprofloxacin, is low but numbers are increasing in each year. High level resistance, to both penicillin and ciprofloxacin, has generally been found among heterosexual men and is often acquired abroad. However, there is some evidence of a change to endemic spread in 2000.
Conclusions: This surveillance programme shows that the epidemiology of gonorrhoea in London is changing with increasing numbers and changing patterns of resistance. If gonorrhoea is to be controlled and targets set by the sexual health strategy are to be met, intervention with effective and appropriate antimicrobial agents is essential.

Concern about the continued increase in sexually transmitted infections (STIs) in the United Kingdom since 1994[1] has resulted in the recent publication of a national strategy for sexual health and HIV.[2] Among the proposed targets is the reduction by 25% of cases of gonorrhoea by the year 2007. Gonorrhoea is the second most common of the bacterial STIs in the United Kingdom and has also risen in numbers with a 27% increase between 1999 and 2000.[3] If transmission of STIs is to be prevented and government targets met significant control measures will need to be implemented. Intervention with antibiotics is an obvious measure for gonorrhoea, where effective therapeutic agents are available, at least in resource rich countries. Surveillance programmes have, however, shown that *Neisseria gonorrhoeae* can develop resistance to most of the therapeutic choices, demonstrated recently with the increasing resistance to the fluoroquinolones.[4]

Gonorrhoea is found predominantly in inner city areas and in England and Wales approximately 50% of gonococcal infections are seen in London.[1] STIs in London are diagnosed primarily at a network of 32 genitourinary medicine (GUM) clinics and control of STIs by rapid diagnosis and effective antibiotics should be a real possibility. However, the incidence of gonorrhoea increased dramatically in London between 1997–9,[5] a rise that continues unabated (unpublished data). Control measures are obviously complicated by the large number of clinics, a mobile and diverse patient population, and by a previous lack of good surveillance data to inform therapeutic choice. A surveillance programme for gonorrhoea in London was established in 1997 to test a representative sample and give a reasonable estimate of the true prevalence of resistance to therapeutic antimicrobial agents.[6] This was the first surveillance programme in England and Wales and in the year 2000 was extended to a national surveillance programme.[7]

In this report we describe the prevalence of resistance in isolates of *N gonorrhoeae* from patients with gonorrhoea attending GUM clinics in London in a 3 month period in each year between 1997 and 2000.

Participants and methods

A surveillance programme was established to collect a representative sample of isolates from consecutive patients with gonorrhoea attending GUM clinics in the North and South Thames regions in 1997. The methodology has been described in detail.[6] Briefly, gonococcal isolates were collected from all patients attending 10 GUM clinics in London for 3 months in each of 4 years, 1997–2000, giving approximately 78% coverage of all gonococcal infections seen in London. The isolates were referred to a single centre and susceptibility was tested to a range of antimicrobial agents used for therapy including penicillin and ciprofloxacin, the recommended and most commonly used first line treatments.[8–10] Isolates were categorised as susceptible or resistant by screening using the agar dilution breakpoint technique and resistant isolates confirmed by determination of the minimum inhibitory concentration (MIC)[6] except for the year 2000 when the MIC was determined for all isolates. Resistant isolates were categorised as penicillinase producing *N gonorrhoeae* (PPNG), penicillinase producing with high level plasmid mediated tetracycline resistant *N gonorrhoeae* (PP/TRNG), chromosomally mediated resistant *N gonorrhoeae* (CMRNG), quinolone resistant *N gonorrhoeae* (QRNG), and isolates with reduced susceptibility to ciprofloxacin (CIP reduced). A limited amount of demographic data was collected on each patient who attended in 1998, 1999, and 2000, including sex, age, site of isolation, foreign travel, and sexual orientation. Statistical analysis was performed using the χ^2 test using Excel (Microsoft).

RESULTS

A total of 6024 gonococcal isolates were collected between 1997 and 2000, of which 4247 (70.5%) were from men and

Table 1 Total number of isolates received and characteristics of patients with gonorrhoea

Year	Total isolates	Male patients		Female patients	
		No (%)	Age range (mean)	No (%)	Age range (mean)
1997	1155	780 (68)	15–60 (28.6)	368 (32)	14–64 (22.1)
1998	1295	918 (71)	15–72* (29.1)	377 (29)	13–55 (22.2)
1999	1559	1139 (73)	14–89 (29.2)	417 (27)	12–51 (22.9)
2000	2015	1410 (70)	14–71 (29.1)	603 (30)	13–53 (22.3)

*Two male patients <15 years of age.

Table 2 Plasmid and chromosomally mediated resistance among gonococci isolated in London between 1997–2000

Year	Number of isolates (%)				
	Total isolates retrieved	PPNG	PP/TRNG	CMRNG	Total penicillin resistance
1997	1133 (98)	6 (0.5)	15 (1.3)	86 (7.6)	107 (9.4)
1998	1203 (93)	10 (0.8)	12 (1.0)	39 (3.2)	61 (5.1)
1999	1523 (98)	14 (0.9)	44 (2.9)	23 (1.5)	81 (5.3)
2000	1979 (98)	64 (3.2)	51 (2.6)	58 (2.9)	173 (8.7)

PPNG = penicillinase producing, tetracycline MIC <16 mg/l; PP/TRNG = penicillinase producing, tetracycline MIC ⩾16 mg/l; CMRNG = non-penicillinase producing, penicillin MIC ⩾1 mg/l, tetracycline MIC 2–8 mg/l.

Table 3 Acquisition of infection abroad among gonococci isolated in London between 1998–2000

Year	Number of isolates (%) acquired abroad/total resistant strains				
	PPNG	PP/TRNG	CMRNG	QRNG	CIP reduced
1998	4/10 (40)	5/12 (42)	3/39 (8)	2/4 (50)	5/8 (63)
1999	7/14 (50)	3/44 (7)	2/23 (9)	10/16 (63)	1/13 (8)
2000	9/64 (14)	6/51 (12)	11/58 (19)	6/20 (30)	7/53 (13)

1765 (29.3%) from women (sex was not recorded in 12 patients). The number of isolates received from the same 10 GUM clinics increased by 74% from 1155 isolates in 1997 to 2015 isolates in 2000 (table 1). There was little variation in ratio of male to female isolates or the mean ages of the patients over the 4 years (table 1). Sexual orientation was known for 3039 (88%) male patients presenting between 1998–2000 and during this period there was no increase in the number of isolates reported from men who have sex with men (MSM), mean 40.9%, range 39.2%–42.4% (p=0.27, NS).

On arrival at the central laboratory 93% or more of the isolates were retrieved for susceptibility testing in each year. Plasmid mediated resistance to penicillin (PPNG, PP/TRNG) was detected in 1.8% of isolates in both 1997 and 1998 but increased in 1999 to 3.7% and again in 2000 to 5.8% (table 2). Sexual orientation was known for 124 of 136 men infected with PPNG or PP/TRNG between 1998 and 2000, of which 106 (86%) were heterosexual. PPNG were acquired abroad in 45% of cases in 1998 and 1999 but in only 14% in 2000. PP/TRNG were only associated with acquisition abroad in 1998 but not in 1999 and 2000 (table 3).

Chromosomal resistance to penicillin (CMRNG) was found among 7.6% of isolates in 1997 but this level decreased to 1.5% in 1999. In 2000 this decline in numbers was reversed with 2.9% of isolates exhibiting chromosomal resistance. Between 1998 and 2000 sexual orientation was known for 102 of 109 men infected with CMRNG, of which 74 (73%) were known to be MSM. CMRNG were not associated with infection known to be acquired abroad (p=0.21, table 3) and were believed to be acquired predominantly in the United Kingdom. Total penicillin resistance (PPNG, PP/TRNG, and CMRNG) has varied but has remained above 5% in all 4 years (table 2).

The incidence of isolates of QRNG encountered has been low ranging from 0.3% in 1997 to 1.0% in 2000, but this represents a fivefold increase in numbers of isolates from four to 20, p=0.03 (fig 1). QRNG were found in 34 men between 1998 and 2000, of which 24 (85.7%) of 28 where sexual orientation

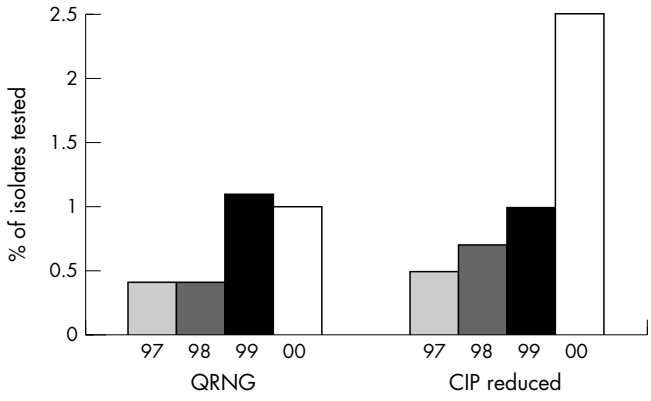

Figure 1 Resistance and reduced susceptibility to ciprofloxacin between 1997 and 2000. QRNG = PPNG, non-PPNG, PP/TRNG or CMRNG, ciprofloxacin MIC ⩾1 mg/l; CIP reduced = PPNG, non-PPNG, PP/TRNG or CMRNG, ciprofloxacin MIC 0.12–0.5 mg/l.

was recorded, were heterosexual. Infection with QRNG was often acquired abroad (table 3). In contrast, isolates exhibiting reduced susceptibility to ciprofloxacin have increased steadily from six (0.5%) isolates in 1997 to 53 (2.7%) in 2000, p=<0.001 (fig 1) and were less commonly acquired abroad in 1999 and 2000 (p=0.6, NS, table 3). Isolates with reduced susceptibility were also associated with infection in MSM, 42 (80.8%) of 52 men for which sexual orientation was known.

DISCUSSION

This collaboration between GUM clinics and laboratories has produced the first longitudinal data on the prevalence of resistance to antimicrobial agents used for the therapy of gonorrhoea in London. The initial observation of a dramatic increase in the number of isolates collected was unexpected but is a phenomenon found throughout the United Kingdom[1 3] and Europe.[11 12] The increase was in all age groups[5] and there was no increase in the proportion of isolates from MSM between 1998 and 2000 which differs from reports from the United States[13] and Australia.[14]

In a large city such as London intervention by rapid diagnosis and effective antibiotics will play a major part in control of gonorrhoea. In this study in London six of the 10 GUM clinics are using amoxycillin (with probenecid) and the remainder are using ciprofloxacin as first line treatment which has remained unchanged since 1997.[6] The results of this surveillance programme have shown that the patterns of resistance among gonococcal isolates in London have changed between 1997 and 2000 which may be a response to therapeutic choice.

High level plasmid mediated resistance to penicillin, due to the production of penicillinase, was at a low level for the first 3 years of this study. The PPNG isolates were often acquired abroad and were found predominantly in heterosexuals, as found by others in the United Kingdom.[15 16] However, in 2000 the prevalence of PPNG and PP/TRNG together rose to 5.8% and were isolated from patients attending all 10 GUM clinics with a prevalence 5% or more in seven of the clinics, the level recommended for changing first line therapy.[9 17] These isolates were less often found in patients who were known to have travelled abroad suggesting possible endemic spread. An increase in a specific group in one year may be the result of an outbreak masked by the large increase in the total number of isolates. However, monitoring of the prevalence of PPNG in future years is essential as treatment of high level plasmid mediated resistance with an inappropriate antibiotic is known to result in therapeutic failure.[16]

Chromosomal resistance to penicillin, which is of a lower level, declined between 1997 and 1999. This decrease in prevalence may have resulted from a removal of the selective pressure of treatment with a penicillin, although treatment regimens remained unchanged in London. The national surveillance programme (GRASP) reported that the majority of out of London clinics were using ciprofloxacin as first line therapy.[7]

In 2000 there was a small increase in CMRNG isolates but the level remains less than 5% of the total. CMRNG isolates were associated with infection in MSM, owing to the increased prevalence of strains carrying the *mtr* mutations among these infections,[18 19] which confers resistance to faecal lipids and aids survival in the rectum ensuring continued transmission. CMRNG isolates are associated with >5% chance of therapeutic failure[20] but are considered less of a problem than PPNG isolates because CMRNG have a lower MIC than PPNG isolates (approximately 1–4 mg/l compared with 8–32 mg/l). The chance of therapeutic failure is related to the MIC of the infecting organism and is greater as the MIC increases. The association of CMRNG with infection in MSM is well established and should not present a problem for therapy unless gonorrhoea increases particularly in this group.

Ciprofloxacin is a recommended alternative for first line therapy[8] and is used by four of the 10 clinics in this study. The level of high level resistance to ciprofloxacin in London is low, which contrasts with levels of resistance found in other parts of the country.[7] In 1998 and 1999 infections with QRNG were often acquired abroad and found in heterosexuals, as reported previously in the United Kingdom.[21 22] Therapeutic failure with QRNG is high[21] and has been largely controlled by identifying infected patients with a recent travel history. However, in 2000 the number of QRNG increased and were less commonly known to be acquired abroad which may reduce the effectiveness of treatment based on travel history.

The drift in reduced susceptibility to ciprofloxacin over the 4 years may be more worrying. These isolates are known to be endemic[23] and to be prevalent among infection in MSM. The MIC that relates to therapeutic failure to ciprofloxacin has been chosen as 1 mg/l or greater, although treatment failures have been documented with isolates with MICs between 0.12–0.5 mg/l[21 22] albeit at a reduced rate.

These results give the first real estimate of the prevalence of antimicrobial resistance in gonococci from a representative sample of consecutive patients in London. The increase in total numbers of isolates and the patterns of resistance indicate that the epidemiology of gonorrhoea in London, as in many other parts of the world, is undergoing change. One of the challenges is to reduce gonorrhoea by effective therapy. Gonococci will develop resistance in response to antibiotic pressure and presumably can maintain sensitivity if the selection is removed. Sufficient dosage of an effective and appropriate antimicrobial agent administered at the earliest opportunity, preferably at the patient's first visit to the clinic, is essential to break transmission. In London, diagnosis and treatment are complicated by a mobile population that attends a network of clinics and hence the necessity for good and continuing surveillance data is paramount. This will be provided, at least until 2004, with the success of the pilot for national surveillance.[7]

LONDON GONOCOCCAL WORKING GROUP

A Robinson, G Ridgway, M. Prince, University College London Hospitals; F Boag, K McLean, A MacOwan, B Azadian, L Willis, Chelsea and Westminster Hospital Trust; M Nathan, A M Karcher, A Hutcheon, Homerton Hospital; M Tenant-Flowers, J Wade, M Graver, King's College Hospital; F Davidson, R Holliman, P Green, St George's Hospital; L Greene, Q N Karim, S Philip, St Mary's Hospital; C Escourt, S Das, R Cooke, G Forster, A Mifsud, D Ball, P Davis, Barts and The London NHS Trust; S Murphy, S Shafi, P Patel, Central Middlesex Hospital; D Barlow, C Warren, C Guest, St Thomas's Hospital; J Russell, A MacKay, G Vosper, Queen Elizabeth Hospital, Woolwich; G Gabriel, N Hutchinson, S Rattenbury, Royal Free Hospital; P Kell, M Kelsey, G Hunsome, Archway/Whittington Hospital.

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CONTRIBUTORS

CAI was responsible for initiating and coordinating the study and for assisting with testing the isolates; IMCM was responsible for the management of the programme, testing isolates, and data analysis; CAI and IMCM shared equal responsibility for preparing the work for publication. The LGWG was responsible for setting up the collaboration and collection of isolates and patient information at each centre and for critical review of the manuscript.

Authors' affiliations
C A Ison, I M C Martin, Medical Microbiology, Department of Infectious Diseases and Microbiology, Faculty of Medicine, Imperial College of Science, Technology and Medicine, St Mary's Campus, London W2 1PG, UK

REFERENCES

1 **PHLS**, DHSS & PS and the Scottish ISD(D)5 Collaborative Group. *Trends in sexually transmitted infections in the United Kingdom, 1990–1999*. London: Public Health Laboratory Service, 2000.
2 **Department of Health**. *The national strategy for sexual health and HIV*. London: DoH, 2001.
3 **CDSC**. Diagnoses of gonorrhoea reach ten-year high. *Commun Dis Rep CDR Wkly* 2001;**11**:30.
4 **WHO Western Pacific Region Gonococcal Antimicrobial Surveillance Programme**. Surveillance of antibiotic resistance in Neisseria gonorrhoeae in the WHO Pacific Region, 1999. *Commun Dis Intell* 2000;**24**:269–71.
5 **Martin IMC**, Ison CA, London Gonococcal Working Group. Rise in gonorrhoea in London. *Lancet* 2000;**355**:623.
6 **Ison CA**, Martin IMC, and the London Gonococcal Working Group. Susceptibility of gonococci isolated in London to therapeutic antibiotics: establishment of a London surveillance programme. *Sex Transm Inf* 1999;**75**:107–11.
7 **GRASP Steering Group**. *The Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP) Year 2000 report*. London: Public Health Laboratory Service, 2001.
8 **Clinical Effectiveness Group**. National guidelines for the management of gonorrhoea in adults. *Sex Transm Inf* 1999;**75** (Suppl 1):S13–15.
9 **Fitzgerald M**, Bedford C. National standards for the management of gonorrhoea. *Int J STD AIDS* 1996;**7**:298–300.
10 **Fitzgerald M**. Antibiotic treatment in the UK. *Genitourin Med* 1997;**73**:149.
11 **Goulet V**, Sednaoui P, Laporte A, *et al*. The number of gonococcal infections identified by the RENAGO network is increasing. *Eurosurveillance* 2000;**5**:2–5.
12 **Van der Heyden JH**, Catchpole MA, Paget WJ, *et al*. Trends in gonorrhoea in nine western European countries, 1991–1996. European Study Group. *Sex Transm Inf* 2000;**76**:110–16.
13 **MMWR**. Increases in unsafe sex and rectal gonorrhea among men who have sex with men—San Francisco, California, 1994–1997. *Morb Mort Wkly Rep* 1999;**48**:45–8.
14 **Donovan B**, Bodsworth NJ, Rohrsheim R, *et al*. Increasing gonorrhoea reports-not only in London. *Lancet* 2000;**355**:1908.
15 **Sherrard J**, Barlow D. PPNG at St Thomas' Hospital—a changing provenance. *Int J STD AIDS* 1993;**4**:330–2.
16 **Young H**, Moyes A, Noone A. Epidemiology and treatment outcome of infection with antibiotic resistant strains of Neisseria gonorrhoeae in Scotland. *Commun Dis Public Health* 1999;**2**:198–202.
17 **McCutchan JA**, Adler MW, Berrie JRH. Penicillinase-producing Neisseria gonorrhoeae in Great Britain 1977–81: alarming increase in incidence and recent development of endemic transmission. *BMJ* 1982;**285**:337–40.
18 **Morse SA**, Lysko PG, McFarland L, *et al*. Gonococcal strains from homosexual men have outer membranes with reduced permeability to hydrophobic molecules. *Infect Immun* 1982;**37**:432–8.
19 **Shafer WM**, Balthazar JT, Hagman KE, *et al*. Missense mutations that alter the DNA binding domain of the MtrR protein occur frequently in rectal isolates of Neisseria gonorrhoeae that are resistant to faecal lipids. *Microbiology* 1995;**141**:907–11.
20 **Jones RN**, Gavan TL, Thornsberry C, *et al*. Standardization of disk diffusion and agar dilution susceptibility tests for Neisseria gonorrhoeae: interpretive criteria and quality control guidelines for ceftriaxone, penicillin, spectinomycin and tetracycline. *J Clin Microbiol* 1989;**27**:2758–66.
21 **Forsyth A**, Moyes A, Young H. Increased ciprofloxacin resistance in gonococci isolated in Scotland. *Lancet* 2000;**356**:1984–5.
22 **Ison CA**, Woodford PJ, Madders H, *et al*. Drift in susceptibility of Neisseria gonorrhoeae to ciprofloxacin and emergence of therapeutic failure. *Antimicrob Agents Chemother* 1998;**42**:2919–22.
23 **Ivens D**, Martin I, Ison C. Neisseria gonorrhoeae in a London sexually transmitted infection clinic not fully sensitive to quinolones: are isolates imported and how effective is ciprofloxacin as first-line therapy? *Int J STD AIDS* 2000;**11**:774–6.